

REMARKS

Claims 1-8 are pending in the above-identified application and stand ready for further action on the merits.

The amendments made herein to the claims do not incorporate new matter into the application as originally filed and at the same time help to resolve issues outstanding, and/or put the claims into a better format for appeal, so that entry thereof is appropriate at present.

For completeness, it is noted that support for the amendment to claim 1, and the recitation of an "outermost layer" therein, occurs at page 6 of the application, lines 9-12.

Examiner Interview

The undersigned greatly appreciates the Examiner's courtesy in both the scheduling and holding of an interview at the USPTO on Tuesday, May 13th, 2003, even though a final office action has issued in the matter of this case. Applicants believe that the interview was helpful to resolving issues outstanding in the matter of the instant case. It is additionally noted that the Examiner's comments in the Examiner Interview Summary form are correct with regard to what was discussed in the Interview.

Claim Rejections Under 35 USC § 102/103

Claims 1-3, 6 and 8 have been rejected under 35 USC § 102(b) as being anticipated by Cardinal (US 4,601,893). Further, claims 4-5 and 7 have been rejected under 35 USC § 103(a) as being unpatentable over Cardinal based upon an allegation of obviousness. Reconsideration and withdrawal of each of these rejections is requested based upon the following considerations.

Rejection Under 35 USC § 102(b)

The Cardinal reference (US 4,601,893) discloses a device with a multi-layer laminate comprising two or more core sheets containing an active agent for controlled release of two or more active agents (Col. 3, lines 15-36; Col. 5, line 53 to Col. 6, line 10). These core sheets are interposed or sandwiched between coextensive inert polymeric films (Col. 3, lines 26-32). Each core sheet can be, but need not be, separated by a coextensive inert polymeric film (Col. 6, lines 11-22). The three layer (sandwich) laminate comprising a single core sheet and two outer films can be rolled into a constrained cylindrical shape for oral administration (Col. 11, line 55 to Col. 12, line 66; Figure 3).

From the teaching discussed above, the device of Cardinal necessitates having a coextensive inert polymeric film as the outmost layer thereof. Cardinal does not teach or suggest that such a coextensive inert polymeric film contains a water-soluble drug dispersed in a carrier. On the other hand, Claim 1 of the present application defines "an outermost layer" to contain a water-soluble drug dispersed in a carrier. Therefore, the preparations defined in Claim 1 (and Claims 2, 3, 6 and 8 depending there from) are not identical to the device of Cardinal in that the outermost layer in the instant invention contains a water-soluble drug.

Concerning the rejection under 35 USC § 102(b), the Examiner has previously remarked that the device of Cardinal is comprised of two or more core sheets for controlled release of two or more active agents. The Examiner might have (a) regarded that "an outermost layer" and "one or more inner layer(s)" as recited in Claim 1, are equivalent to the "two or more core sheets" of the device of Cardinal, and then (b) conceive that the instantly claimed preparation could further comprise a coextensive inert polymeric film outside "an outermost layer", since Claim 1 defines the preparation using the transitional phrase "comprising". However, according to such an interpretation of Claim 1, it is apparent that such a coextensive inert polymeric film would have to in turn serve as "an outermost layer" when it is located outside

the currently recited "outermost layer" in which case the "coextensive inert polymeric film" must contain a water-soluble drug, since the claims under consideration require no less.

Cardinal actually teaches a device with a multi-layer laminate comprising two or more core sheets containing a drug. However, such a device is formed by rolling a multi-layer laminate into a constrained cylindrical shape (see Col. 11, lines 66-68). On the other hand, in the present invention, each layer of the preparation is separately or simultaneously prepared in a mold to form a rod-like shape (see page 12, line 8 to page 13, line 5). The device as shown in Fig. 4 of the Cardinal reference is not a rod-like shaped device, but a ring-shaped device (Col. 5, lines 10-13). The device as shown in Fig. 3 of Cardinal may be referred to as having a rod-like in shape as pointed out by the Examiner, however, such a device comprises each layer located vorticosely in the diametrical direction of the device. In contrast, as shown in Fig. 1 and defined in Claim 1 of the present application, the preparation of the invention is a rod-like shape preparation comprising an outermost and inner layer(s) concentrically located in the diametrical direction of the preparation. Thus, the rod-like preparations defined in Claim 1 (and Claims 2, 3, 6 and 8 depending there from) are quite different from the device of Cardinal in both their rod-like shape and the resulting configuration, with the

drug-containing layers being concentrically in the diametrical direction in the instant invention.

In the outstanding Office Action at page 5, lines 2-4, the Examiner states as follows:

"...Applicants attempt to distinguish over the prior art by describing one of the drug layers as the outer layer. That layer is the outer drug layer relative to the inner layer.

By amending claim 1 (and claims 2, 5 and 7) herein to provide for an "outermost layer", the above comments are submitted to be rendered moot, to the extent that they are being used to support the outstanding rejection of the pending claims.

In the outstanding Office Action at page 5, lines 4-6 the Examiner states as follows:

"...Again, nothing in the instant claims excludes the additional inert polymer film from being part of the composition. Further, applicant has not shown that such a layer would have a detrimental effect on the present invention."

Because the drug formulations of the instant invention have an outermost layer as defined in the claims, their construction enables and allows for controlled drug release in diverse ways, wherein different kinds of drugs or different concentrations of the same drug can freely provide a complex release behavior. (Please see page 13, line 6 to page 14, line 6 of the instant application.) Still further, such effects of the inventive compositions are

evidenced and exemplified at page 14, line 7 to page 16, line 21 of the specification.

In contrast, in the drug formulations taught by Cardinal, release of a water-soluble drug is limited to that from a surface of a core sheet, which is sandwiched between two impermeable films, exposed to the use environment. Accordingly, the formulation of Cardinal does not have potential to provide a complex release behavior as is achieved by and controlled precisely by the drug formulation of the instant invention. As such using the impermeable films of Cardinal in the present invention would not have allowed the inventors to discover the solution to the problem they strove to solve (see page 3 lines 21-22 of the instant specification). The fact that the Examiner has also failed to recognize the detrimental effect of the impermeable films of Cardinal on the ability of the inventive compositions to solve the problem of providing a formulation having "a complex release behavior" is submitted to be *per se* evidence of both the non-obviousness and patentability of the instant invention over Cardinal.

At page 5, lines 7-18 of the outstanding office action, the Examiner states as follows:

"... [A]pplicants argue that the prior art device and the instant invention are made by different processes and that the multiple layer are located vorticosely in the diametrical direction as opposed to concentrically in the diametrical direction."

"The Examiner would like to point out that the instant claims are drawn to composition type claims and the process of making limitations are not found in the claims. Therefore, arguments drawn to the process of making the device are irrelevant. Further, while Figure 3 of the prior art shows a rolled up device in which the ends overlap to form layer in what applicants called vorticosely located layers, there is nothing in the prior art that states this is the only way to roll such a device. It is possible to roll a device that has two drug layers in a way so that the ends join together but do not overlap thereby forming a device where the drug layers are located concentrically in a diametrical direction. Therefore, applicants' argument to the contrary is unpersuasive."

Applicant's arguments filed on November 27, 2002 did not intend to solely distinguish the drug formulation of the instant invention from that of Cardinal by the process of making the drug formulation. Instead, as already pointed out the drug formulations of the instant invention are quite different from the teachings of Cardinal in their composition.

In the outstanding Office Action (see page 5 lines 14-15 quoted above), the Examiner states "there is nothing in the prior art that states this is the only way to roll such a device." However, even if this is true, the Examiner has not pointed to any specific disclosure in Cardinal, or any other art, that would have motivated one of ordinary skill in the art to arrive at the invention as claimed.

Thus, while typically an Examiner will point to specific disclosure in an application to support an anticipation or

obviousness rejection of a claim, in the present case the Examiner has not done so. Instead, the Examiner simply indicates that in the teachings of Cardinal "there is nothing ... that states this is the only way to roll such a device." It is submitted that such a bare statement of a references non-teaching cannot properly support a either an anticipation rejection or *prima facie* case of obviousness.

Apart from the above considerations, a through review of the cited Cardinal et al. reference makes clear that the cylindrical constructions taught therein, such as those provided in Figure 3 thereof, are used to facilitate easy oral administration to a ruminant, with the provided cylinder being restored to a substantially rectangular shape (i.e., the cylinder unrolls when swallowed by a ruminant) to permit retention of the device in the rumeno-reticular sac (rumen) of a ruminant (see column 11, line 63 to column 12, line 6).

As such, in actual use the "cylindrical" compositions and constructions of Cardinal are quite different from the rod-like compositions of the present invention, in both their initial appearances and in their intended configurations during use.

Rejection Under 35 USC § 103

The Examiner has rejected claims 4, 5 and 7, assuming that the difference between the inventions of these claims and that of Cardinal would be obvious to a person skilled in the art. That is, it appears that the Examiner regards that incorporation of two or more active agents into a single layer and incorporation of the same active agent into different layers at different concentrations are obvious to a person skilled in the art.

The invention of Cardinal is directed to a laminate device with multiple layers (see Col. 1, lines 18-20). As discussed above, Cardinal teaches that a laminate with multiple layers is rolled to form a constrained cylindrical device (see Col. 11, lines 66-68). However, such rolling of the laminate inevitably results in multiple layers located vorticosely in the diametrical direction of the device. On the other hand, the rod-like preparation of the invention, as defined in Claim 1, comprises the outermost and inner layer(s) located concentrically in the diametrical direction. Thus, the preparation of the invention could not be obtained so long as a person skilled in the art follows the teaching of Cardinal, regardless of whether or not incorporation of two or more active agents into a single layer or incorporation of the same active agent into different layers at different concentrations would be obvious.

Claims 4, 5 and 7 depending on Claim 1, define a rod-like preparation as comprising each layer located concentrically. Therefore, the inventions of these claims are not obvious over Cardinal.

Furthermore, as discussed above, the outermost layer of the device of Cardinal is a coextensive inert polymeric film. For the coextensive inert polymeric film, Cardinal teaches that it should be "inert", "substantially impermeable to the use environment" and "substantially impermeable to an active agent" (Col. 5, lines 37-42). From these teachings, a person skilled in the art would not be motivated to incorporate an active agent into a coextensive inert polymeric film, because it is expected that the active agent, when dispersed in the coextensive inert polymeric film, would adversely affect the desired property of the film (for example, the "inert" property might be negatively affected by an addition of an active agent, or the "substantially impermeable" property thereof might be negatively affected by channel formation in the film that results from the release of the active agent, as described at page 2, lines 5-16 of the present specification). Therefore, a person skilled in the art is taught away from adding an active agent to the inert polymeric film, by the description of the film in Cardinal, as explained above.

On the contrary, in the outermost layer of the preparation of the invention of claim 1, a water-soluble drug dispersed in a

carrier. Therefore, the invention of Claim 1 is not obvious over Cardinal, and the inventions of claims 4, 5 and 7, depending there from are not obvious.

Additional Comments

The following comments are presented in response to concerns made by the Examiner in the earlier held personal interview held on Tuesday, May 13th, 2003.

1. "Hydrophobic Polymer"

The "outermost layer" of the present invention comprises both of "a hydrophobic polymer material" and "a water-soluble drug" dispersed in the carrier. By virtue of the construction, the release process as described in page 2, lines 5-14 of the present specification occurs, and therefore, the water-soluble drug is released. Actually, as shown in Figures 2 and 3 of the present specification, the formulation of present invention releases sufficient amount of a water-soluble drug.

Therefore, even though the "polymer" used for the outermost layer is hydrophobic, the "outermost layer" in which a water-soluble drug is dispersed, as a whole, can sufficiently release a drug. The person skilled in the art of implantable sustained release formulation understands it based on his/her knowledge of the art and the description of the present specification.

2. "Fujioka US 5,581,547"

The claims of the present invention are novel over Fujioka '547, as the outer layer of Fujioka '547 does not contain a water-soluble drug.

As for obviousness, although the Examiner has not established a prima facie case yet, the following reasons are presented as to why the present invention is unobvious, for purposes of expediting prosecution towards allowance.

As Fujioka '547 discloses at column 4, lines 7-8, as "outer layer is impermeable to water", the "outer layer" itself is impermeable to water, in contrast to the outermost layer of the present claims explained above. Therefore, the formulation of Fujioka '547, by virtue of the impermeability of the outer layer as a whole, limits the water infiltration to an optimal regulation (column 4, lines 19-20), that ultimately enables the release at a nearly constant rate ("releases a water-soluble drug...at a nearly constant rate", column 3, lines 62-64). As a person skilled in the art of implantable sustained release formulation should understand, such a role of the outer layer of the Fujioka '547 formulation, he/she is taught away from dispersing a water-soluble drug into the outer layer.

Further, the problem to be solved by the present invention itself is found by the inventors (see page 3, lines 21-22 of the

present specification). The application of the formulation of the present invention such as exemplified at page 14, line 7 to page 16, line 21, is found by thorough investigation of a new application of an implantable sustained release formulation. Without such a finding, the problem to be solved cannot be found and the present invention should not be made without such a recognition of the problem to be solved. Therefore, the present invention is not obvious from Fujioka '547.

Accordingly, the Examiner has failed to show any teachings in the cited art of Cardinal, or any other cited art, that would motivated one of ordinary skill in the art to arrive at the present invention as claimed.

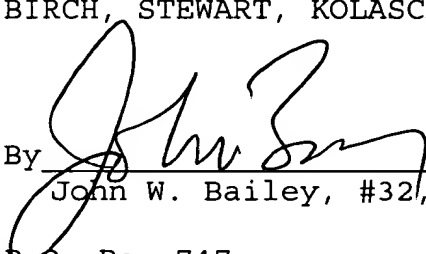
CONCLUSION

Based upon the above remarks, and the arguments set forth therein, Applicants respectfully request that the Examiner now issue a Notice of Allowance clearly indicating that each of Applicants' pending claims 1-8 are allowed and patentable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees. Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 
John W. Bailey, #32,881

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

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0020-4771P

VERSION WITH MARKINGS TO SHOW CHANGES MADEIN THE CLAIMS:

1. (Amended) A preparation which comprises an [outer] outermost layer wherein a water-soluble drug is dispersed in a carrier comprising a biologically non-degradable hydrophobic polymer material, and one or more inner layer(s) wherein a water-soluble drug, which is different or different in concentration thereof from the drug contained in the [outer] outermost layer, is dispersed in a carrier comprising a biologically non-degradable hydrophobic polymer material, and in which the [outer] outermost and inner [layers] layer(s) are concentrically located in diametral direction of a rod-like preparation, [and] both or one of the ends in axial direction are open so as to directly come into contact with the environment and the outermost layer directly contacts with the environment in the diametrical direction.

2. (Amended) A preparation as claimed in claim 1 wherein a layer consisting of only biologically non-degradable hydrophobic polymer material exists between the inner [layer] layers in which a water-soluble drug is dispersed and the [outer] outermost layer, or between two inner layers in which a water-soluble drug is dispersed.

5. (Twice Amended) A preparation as claimed in claim 1, wherein at least one of the [outer] outermost layer or inner layer(s) contains two or more drugs.

7. (Amended) A preparation as claimed in claim 2, wherein at least one of the [outer] outermost layer or [inner(s)] inner layer(s) contains two or more drugs.